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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/706,325	11/03/2000	Juan M. Zapata	P-LJ 4453	6212

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/706,325	ZAPATA ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *8-11,46 and 68-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *9, 10, 77-82, 84, 85* is/are allowed.

6)☐ Claim(s) *8,11,46,68-76,83 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-7, 12-45, 47-67 have been canceled. claim 69 has been amneded. Claims 84-98 have been added. Claims 8-11, 46, 68-98 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Grounds of Rejection

Claims 8, 11, 46, 68, 69-72, 74-76, 83 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Everett et al (The EMBO Journal, 1997, Vol. 16, pp. 1519-1530)

Claim 8 is drawn to an isolated anti-TPBD antibody which has specific reactivity with a TRAF-protein binding domain amino acid sequence of SEQ ID NO:19. Claim 11 embodies the antibody of claim 8 wherein said antibody is polyclonal. Claim 46 is drawn in part to a therapeutic composition comprising an isolated anti-TPBD antibody which specifically binds a TPBD sequence selected in part from the group consisting of SEQ ID NO:8, 19 and 20 in a pharmaceutically acceptable carrier. Claim 68 is drawn to an isolated anti-TPBD antibody which has specific reactivity with a TRAF-protein site of a TPBD amino acid sequence selected from the group consisting in part of SEQ ID NO:8, 19 and 20 and wherein said antibody modulated the association of a TPBD with a TNF family receptor, TRAF protein or a TRAF-associated protein. Claim 70 embodies the antibody of claim 69 wherein said TNF family receptor is TNF-R2, said TRAF protein is human TRAF6 and said TRAF-associated protein is I-TRAF. Claim 71 embodies the antibody of claim 69 wherein said TNF-family receptor is CD40, said TRAF protein is human TRAF2 and said TRAF-associated protein is I TRAF. Claim 72 embodies the antibody of claim 69 wherein said antibody inhibits the association of said TPBD with said TNF family receptor, TRAF protein or TRAF-associated protein. Claim 74 embodies the antibody of claim 8 wherein said antibody specifically binds to a TPBD amino acid selected from the group consisting of SEQ ID NO:8, 12, 23 or 24. Claim 76 embodies the antibody of claim 75 wherein said antibody specifically reacts with SEQ ID NO:8. Claim 83 embodies the antibody of claim 75 wherein said antibody is polyclonal. Claim 86 embodies the antibody of claim 76 wherein said antibody is polyclonal.

Everett et al disclose a polyclonal serum, r29, which was raised to HAUSP residues 28-427. The instant SEQ ID NO:8 is identical to HAUSP residues 58-196 of the Herpesvirus associated ubiquitin specific protease as evidenced by the attached sequence alignment with Accession Number Q93009. It would be reasonable to conclude that the r29 polyclonal antiserum included antibodies which specifically bound to the TRAF protein binding site. It is noted that both SEQ ID NO:8 and SEQ ID NO:19 comprises the sequence motif of LXWXXXVP which is SEQ ID NO:20. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 69-71 and 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies which decrease or inhibit the association of a TPBD with a TNF family receptor, TRAF protein or a TRAF-associated protein, does not reasonably provide enablement for antibodies which increases the association of TPBD with a TNF family receptor, TRAF protein or a TRAF-associated protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 69 is drawn to an antibody which modulates the association of a TPBD with a TNF receptor, TRAF protein or a TRAF-associated protein. Claims 70 and 71 carry the same limitation of "modulates". claim 73 embodies the method of claim 69 wherein the antibody increases the association of said TPBD with said TNF family receptor, TRAF protein or a TRAF associated protein.

The instant specification teaches that TRAF is a Tumor Necrosis Factor Receptor Associated Protein which is involved in the intracellular signaling of the TNF receptor. The specification has identified TRAF Protein Binding Domains (TPBD) which are responsible for interaction with TRAF. The instant claims are drawn to antibodies which specifically "react"

with said TRAF Protein Binding Domains. Claims 69-72 carry the limitation wherein the binding of the antibody modulates the association of the TPBD with TNF receptor, TRAF or a TRAF-associated protein. Claim 69 states that the modulation is an increase in the association of TPBD with TNF receptor, TRAF or a TRAF-associated protein. The art recognizes that ant antibody bound to a substrate constitutes an physical blockage to the epitope on the substrate to which the antibody is bound. The TPBD-antibody complex would no longer have the TPBD available for interaction with other proteins. One of skill in the art would conclude that the binding of an antibody to a TPBD could not result in an increased interaction between proteins which normally bind this domain and the TPBD. the specification does not give any guidance as to how to design an antibody which would be present on the TPBD and at the same time increase the interaction of the protein with other proteins which bind to the TPBD. Given this lack of teaching in the specification, one of skill in the art would be subject to undue experimentation in order to make the invention wherein the binding of the antibody results in increased interaction between the TPBD and TNF receptor, TRAF and TRAF-associated proteins.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 46 is drawn to a therapeutic composition comprising an antibody having specific reactivity with a TPBD selected from the group consisting of SEQ ID NO:8, 12, 19, 20, 21, 22, 23, 24 and 25 and a pharmaceutically acceptable carrier. The specification teaches that the TPBD of the invention have been identified from newly identified TRAF proteins (page 8, lines 22-24) and that TRAF proteins are intracellular proteins (page 9, lines 19-23). Claim 46 carries the specific limitation of "therapeutic composition" which would require the administration of said composition for the indication of a therapeutic response. It is unclear how an antibody which would specifically bind the instant TPBD could be used as a therapeutic composition. In order for the antibody to bind to TRAF, the intracellular domain of the TNF receptor or a TRAF-associated protein it must necessarily be in the cytoplasm of the cell. It is recognized that TNF receptor is internalized upon binding of TNF to the extracellular domain of the receptor. However, the instant

antibodies are binding the TRAF-protein binding domain of the TNF receptors which is located intracellularly. Thus, the antibody would bind to the external domain of the TNF-receptor and would not be internalized. Therefore, it would not be expected that the antibody would be able to contact the TPBD in the cytoplasm of the cells. Further, Seaver (Genetic Engineering News 1994 Vol 14, No 14: pages 10 and 21) teaches that "selection of the final antibodies [for clinical application] requires work with real clinical specimens" to ensure selection of a monoclonal antibody that has the specificity necessary for binding to the targeted substrate under conditions where many cellular proteins are present (see fourth column, first full paragraph). Applicant should note that the real sample may contain structurally related substances of the target., and that antibodies often bind to three dimensional epitopes which do not comprise a linear amino acid sequence.

All other rejections and objections as set forth in Paper No. 7 are withdrawn in light of applicants arguments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
November 17, 2003